REMARKS

Applicants respectfully requests entry of the amendments and remarks submitted herein. Claims 1-12 have been amended and are currently pending. Attached is a marked-up version of the changes being made by the current amendments. Reconsideration of the pending application is respectfully requested.

Sequence Listing

The Examiner has indicated that the present application fails to comply with the requirements of 37 C.F.R. §1.821 – §1.825.

Applicants submitted a paper copy and a computer readable form of the Sequence Listing on February 19, 2002 in response to the Notice To File Missing Parts mailed August 21, 2001. It is believed that the application complies with the requirements of 37 C.F.R. §1.821 – §1.825.

The 35 U.S.C. § 101 Rejections

Claims 1-12 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-12 have been amended to recite "an isolated nucleotide sequence." Therefore, Applicants respectfully request that the rejection of claims 1-12 under 35 U.S.C. §101 be withdrawn.

The 35 U.S.C. § 112 Rejections

Claims 1 and 9-12 stand rejected under 35 U.S.C. § 112, first paragraph, as the Examiner asserted that those claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

In rendering this rejection, the Examiner purports that the specification fails to teach which fragments are functional promoters. Furthermore, the Examiner deems that the

specification fails to teach whether other 9 kb fragments outside this region can also promote villin gene transcription.

Applicants submit that the relationships between the 9 kb promoter fragment from –3.5 to +5.5 and its function are sufficiently described in the present specification. More specifically, the present invention relates to regulatory (promoter) sequences of the mouse villin gene that drives the expression of villin in immature and differentiated epithelial cells of the intestine and urogenital tracts. Methods to test the regulatory activity of promoter fragments are set forth in the examples of the present invention.

Indeed, Applicants submit that the function of promoters was well known in the art at the time of filing this application, i.e., a promoter was known to be a DNA sequence located 5' of a gene that initiates transcription. Furthermore, a person skilled in the art had the knowledge and tools for isolating promoters at the time the application was filed. Therefore, a detailed description is not necessary to satisfy the written description requirement, since this is common general knowledge.

Indeed, it was known since the early 1980's, that, in eukaryotic organisms, a promoter sequence comprised at least a TATA box that is centered around nucleotide position 25 and has the consensus sequence 5'-TATAAAA-3', and a CAAT box around nucleotide position 90 with the consensus sequence 5'-GGCCAATCT-3.'

Furthermore, Applicants submit that the skilled artisan at the time of filing this application could rely on reviews or books forming part of the general knowledge in the field of the invention, e.g., in Lewin et al. (1990, *Genes IV*, Oxford University Press). Therefore, identifying and evaluating functional promoter fragments within the 9 kb mouse villin promoter was well within the knowledge of the skilled artisan, and the specification also provides sufficient guidance to identify and evaluate functional fragments. For example, the examples in the present specification set forth ways in which the regulatory activity of fragments can be tested.

Indeed, the boundaries of the sequence constituting the mouse villin promoter can be determined by reducing the length of the fragment from either end, until at some point, the promoter ceases to drive transcription. The upstream boundary of the promoter can be identified by progressively removing material from this end until the promoter function is lost. To test the

downstream boundary of the promoter, it is necessary to reconnect the shortened (truncated) promoter to the sequence to be transcribed. The downstream boundaries of a promoter are identified when the promoter function is lost. Promoter deletion analysis is a commonly known procedure to evaluate and characterize promoter activity and has been used successfully to evaluate and characterize numerous promoters prior to the filing of this application.

Indeed, the Written Description Guidelines require that when issuing a rejection for lack of written description, a review of the entire application is made. According to the Written Description Guidelines, "[s]uch a review is conducted from the standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art." When rendering this rejection, it appears that the Examiner did not assess the level of skill and the knowledge of the art at the time of filing of this application. By failing to do so, the Examiner has not met the burden required.

Applicants submit that a lack of written description has not been established and, therefore, this rejection cannot be maintained. Applicants respectfully request that the rejection of claims 1 and 9-12 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1-12 stand rejected under 35 U.S.C. § 112, second paragraph, as the Examiner asserted that those claims were indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The Examiner asserted that the word "derived" in claims 1-12 renders those claims indefinite because the nature and the number of derivative processes are unknown. Applicants have amended claims 1 and 12 to replace "derived" with "obtained."

The Examiner purported that the phrase "having a size of 9 kb on an agarose gel" in claim 1 renders claims 1-12 indefinite since the size of the nucleotide sequence is unclear. Applicants submit that the size of the nucleotide sequence is deduced from the band visualized on an agarose gel as explained, for example, on page 4, line 27 in the present application. Furthermore, the skilled artisan knows that agarose is an uncharged component consisting of repeating 1,3-linked beta-D-galactopyranose and 1,4-linked 3,6-anhydro-alpha-L-

galactopyranose units and containing small amounts of ionized sulfate and pyruvate groups. A gel is formed by heating and cooling the agarose. Since agarose is known in the art and used routinely by scientists, one of ordinary skill in the art could easily identify a 9 kb band on an agarose gel. Therefore, Applicants submit that claims 1-12 are definite in reciting "having a size of 9 kb on an agarose gel."

The Examiner stated that claims 6 and 8 are indefinite for the use of "at around" or "from around" because it is unclear to what position Applicants are referring. Applicants have amended claims 6 and 8 to remove the recitation of "around."

The Examiner purported that the recitation of "nucleotide fragment extending...to the transcription site and further comprises the translation start site" renders claim 7 indefinite because it is unclear which elements this nucleotide fragment comprises. Applicants have amended claim 7 to clarify what is being claimed. As amended, the sequence of claim 7 encompasses the 9 kb fragment, which includes the -3.5 kb fragment up to the transcription initiation site, the transcription initiation site, the translation initiation site, and the 5.5 kb intron between the transcription initiation site and the translation initiation site. Therefore, claim 7 as amended is not indefinite.

In view of amended claims and remarks above, please withdraw the rejection of claims 1-12 under 35 U.S.C. §112, second paragraph.

CONCLUSION

Applicants ask that all claims be allowed. Enclosed is a $205 check for a Petition for Two-Month Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: June 30, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 13-31 have been canceled without prejudice. Claims 1-12 have been amended as follows:

1. (Amended) An isolated nucleotide [Nucleotide] sequence obtained [derived] from the 5' sequence of [the] a murine villin gene, having a size of 9 kb on an agarose gel, or a fragment thereof, comprising [the] nucleotide elements having a cis-regulatory activity that promotes [the] transcription of the murine villin gene.

2. (Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which is the sequence extending 5.5 kb upstream and 3.5 kb downstream from the transcription initiation site of the murine villin gene.

3. (Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which is the sequence identified as Seq ID NO:1.

4. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which comprises the nucleotide fragment extending from the HS I to the HS IV Dnase I-hypersensitive sites.

5. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, comprising a nucleotide fragment extending from the HS IV Dnase-hypersensitive site to the translation initiation site of the murine villin gene.

6. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which comprises a nucleotide fragment extending from the nucleotide at [around] position -100 upstream from the transcription initiation site, to the translation initiation site.

7. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which comprises a 9 kb nucleotide fragment extending from a –3.5 kb nucleotide sequence upstream from the transcription initiation site to the [transcription] translation initiation site (ATG) which includes [and further comprises] the transcription [translation] initiation site and a 5.5 kb intron.

8. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which comprises a nucleotide fragment extending from [around] the nucleotide at position -480 from the transcription initiation sequence, to the translation initiation site.

9. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which is the sequence extending 3.5 kb upstream from the transcription initiation site to the translation initiation site, provided the region corresponding to intron 1, located between said sites, is deleted[,] or deleted in part.

10. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1 which is mutated by deletion of one or several nucleotides[,] within the nucleotide fragment of 5.5 kb corresponding to intron 1 extending from position 47 starting from the transcription initiation site, provided that said mutation does not affect the presence of the HS II Dnase I-hypersensitive site.

11. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which comprises nucleotide regions having a regulatory activity affecting the level of expression of the murine villin gene.

12. (Twice Amended) The isolated nucleotide [Nucleotide] sequence according to claim 1, which is obtained [derived] from the nucleotide sequence of the murine villin gene having a size of 9 kb on an agarose gel and extending 3.5 kb upstream from the transcription initiation site and 5.5 kb downstream from said site, or a fragment thereof, said nucleotide sequence or fragment thereof having a regulatory activity on the level of expression of the murine villin gene in intestine cells and/or in transgenic mice.